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A REVIEW

Impact of vitamin D status during gestation period on low birth weight

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ABSTRACT **:** Low birth weight has been defined by the World Health Organization (WHO) as weight at birth of less than 2,500 g. From conception to birth, the weight of human fetus increases six millions. This rapid growth requires a continuous supply of energy and nutrients which the fetus is unable to synthesize. Maternal socio-economic status, mother's nutrition and diet, lifestyle and other exposures including disease or complications such as hypertension can affect fetal growth and development. Maternal malnutrition causes birth weight reduction. A positive correlation has been seen between maternal and child vitamin D levels. Maternal vitamin D deficiency in early pregnancy has been associated with elevated risk of preterm birth or low birth weight. Low maternal vitamin D status may also slow neonatal cardiac development and alter brain morphology of infant. More recent studies may support the use of vitamin D supplementation during pregnancy to prevent LBW. Maternal total serum calcium levels decline as the pregnancy progresses but during the third trimester, the fetus maintains higher serum calcium levels as a result of active transport of the mineral across the placenta which leads to the low level of calcium in mother. Women at risk of vitamin D deficiency should be monitored and treated during pregnancy for vitamin D deficiency. LBW continues to be a problem of concern as disorders related to LBW and preterm birth are the leading causes of infant mortality. Studies are needed to investigate vitamin D requirements during pregnancy to derive guidelines for health professionals.

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Two forms of vitamin D exist in nature which includes cholecalciferol (Vitamin D_3) from animal sources and ergocalciferol (Vitamin D_2) from plant sources. but in humans, vitamin D is found in form of calciferol (25(OH)D) which includes both 25(OH)D_2 and 25(OH) D_3 and 1,25$(OH)_2$D is the active form of vitamin D which includes both 1,25 $(OH)_2D_2$ and 1,25 $(OH)_2D_3$.

Beneath the skin, cholesterol precursor (7-dehydrocholesterol) is present. When skin exposes to ultra violet radiation, conversion of 7- dehydrocholesterol to previtamin D_3 takes place. Further, previtamin D_3 converts in vitamin D_3 (cholecalciferol) which goes into the circulation bound with vitamin D binding protein (Hollick *et al.*, 1980). Vitamin D may also be consumed from mouth as part of the diet or supplements. Dietary vitamin D may be in the form of ergocalciferol, derived from plants or

cholecalciferol derived from milk, salmon, sardines etc. Both sunlight-derived (vitamin D_3) or ingested (vitamin D_2 or vitamin D_3) vitamin D are transported to the liver where 25-hydroxylase enzymes catalyze conversion to primary storage form 25-hydroxyvitamin D (25(OH)D). Conversion to active form of the hormone requires a further hydroxylation in the kidney, under the control of a 1α-hydroxylase, forming 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). This step is under tight feedback control that is dependant on the body's calcium requirements. A wide range of tissues possess 1α-hydroxylase enzyme, so that local conversion of 25(OH)D to the active $1,25(OH)_2D$ may occur (DeLuca and Zierold, 1998). The active form of vitamin D plays an important role to maintain serum calcium levels with parathyroid hormone (PTH). $1,25(OH)_2D$ increases intestinal calcium absorption and calcium reabsorption from renal tubules and suppresses PTH secretion and encourages mineralization of bones.

Non-calcitropic actions of vitamin D :

Non-calcitropic actions of vitamin D includes stimulation of insulin production (Chiu *et al.*, 2004), thyroid stimulating hormone secretion (Smith *et al.*, 1989) and improve myocardial contractility (Achinger and Ayus, 2005). $1,25(OH)_2D$ also has a range of non-calcitropic functions, with locally synthesized hormone acting through both paracrine and autocrine signaling (Maalouf, 2008). $1,25(OH)_2D$ is an important immunomodulator, potentiating antimicrobial peptide (cathelicidin) activity in human monocytes (Deluca and Cantoma, 2001) and strengthening innate immunity. There are also effects on adaptive immune function, with attenuation of T lymphocyte proliferation and antigen specific activation (Eisman *et al.*, 1989).

Low birth weight :

Low birth weight has been defined by the World Health Organization (WHO) as weight at birth of less than 2,500 grams (5.5 pounds) (WHO, 1992). This cut-off is based on epidemiological observations that infants weighing less than 2,500 g are approximately 20 times more likely to die than heavier babies (Kramer, 1987). In developing countries, a birth weight below 2,500 g may be an outcome of many health problems. Low birth weight is either the result of preterm birth (before 37 weeks of gestation) or of restricted fetal (intrauterine) growth (Kramer, 1987). There are several factors, influencing birth weight like Maternal nutrition (45%), Genetic characteristics including race (25%), maternal height, age, pre-pregnancy weight and previous delivery of low birth weight infant, maternal socio-economic status, mother's nutrition and diet, lifestyle (e.g., alcohol, tobacco or drug abuse) and other exposures (e.g., malaria, hiv or syphilis), or complications such as hypertension can affect fetal growth and development. Maternal malnutrition causes birth weight reduction.

Fetal growth :

From conception to birth, the weight of human fetus increases six millions, cell numbers multiplies to 2000 billions while the amount of water, protein fat and mineral increases one to two billion fold. Fetal growth needs nutrients from outside source which is fulfilled by placenta. It provides nutrients for fetal growth. Analysis of the mineral content of the fetus shows retention of calcium, phosphorus and magnesium with increasing gestational age consistent with skeletal growth. The calcification of the fetal skeleton begins at about 8 weeks. About 80 per cent of fetal mineral accretion occurs after 25 weeks with peak accretion occurring from 34 to38 week's gestation. 80 per cent of the total phosphorus is also in the bone with concentrations increasing along with calcium (Blackburn, 2013).

Factors associated with bone mineralization of fetus:

Fetal responses during gestation are determined by the maternal environment, health, and physiology. Factors associated with alterations in bone mineralization of fetus are as follows :

Season :

There is seasonal changes in vitamin D metabolism which can further influence fetal bone metabolism also. Vitamin D is essential for mineral homeostasis and adequate bone mineralization. A lack of vitamin D during pregnancy may adversely affect maternal mineral metabolism, which in turn could affect the fetal mineral accretion which is thought to be derived from the maternal skeleton (McGrath *et al.*, 2005).

Small for gestational age :

Low weight relative to gestation (SGA or intrauterine growth retardation) could bring alterations in placental mineral transfer. So, it can influence fetal bone metabolism (Namgung *et al.*, 1994).

Infants of diabetic mothers :

Maternal diabetes could be a factor influencing fetal bone metabolism, through alterations in maternal mineral metabolism or limited mineral availability in a pregnancy. (Strand and Ehrenkranz, 1994).

Other factors :

Anthropometric measures, race, gender and maternal ethanol consumption and smoking are also associated with mineralization of bones.

Skeletal growth of fetus :

Skeletal growth is a complex process that begins *in utero* and continues into early adulthood (Kimball *et al.*, 2008). During period of skeletal development and rapid growth, calcium and vitamin D play major role. As a requirement of skeletal growth, fetal calcium accretion starts mid-gestation and increases into the third trimester when the greatest amount of fetal calcium accretion occurs (Kovacs *et al.*, 2005). For instance, fetal accrual of calcium has been found to increase from approximately 50 mg/day at 20 weeks gestation to 330 mg/day at 35 weeks gestation, averaging around 250 mg/day for the third trimester (86,87). It is important that the maternal supply of minerals across the placenta is sufficient to match these accretion rates. To accommodate increased requirements for calcium, maternal intestinal absorption of calcium rises and reaches a maximum in the last trimester (Cross *et al.*, 1995). Throughout this process, elevated serum $1,25(OH)_2D$ concentrations, with appropriate dietary calcium intakes, increase calcium absorption to account for calcium transfer to the fetus (88). It has been noted that calcium absorption efficiency approximately doubles in pregnancy, starting as early as 12 weeks of gestation (89,90). In addition to increased calcium absorption, the maternal skeleton may act as a reservoir of calcium. Indeed, both formation and resorption, indices increase from early gestation by 50–200 per cent by the end of pregnancy, indicating a dynamic response by the maternal skeleton to fetal growth demands. Maternal adaptation to increased calcium requirements is modulated by increased concentrations of $1,25(OH)_2D$.$1,25(OH)_2D$ levels are increased from the beginning of pregnancy through up-regulation of renal and placental 1-~-OHase and extrarenal synthesis. In fact, $1,25(OH)_2D$ concentrations during the second trimester can more than double in comparison with pre-pregnancy values and can increase by 100 per cent during the third trimester. During the third trimester, there is an increase in the amount of free $1,25(OH)_2D$ in both mother and fetus, suggesting that increased concentrations of free $1,25(OH)_2D$ are important to fetal growth and development.Increased serum $1,25(OH)_2D$ concentrations have been positively associated with intestinal calcium absorption during late pregnancy. It is known that vitamin D transport occurs mainly through the placenta in the form of 25(OH)D. At birth, serum 25(OH)D concentrations in the mother correlate with those of the fetus, with cord levels approximating 80 per cent of maternal concentrations (Koo and Tsang, 1984). Adequate maternal vitamin D status during pregnancy is important for neonatal calcium metabolism. In fact, neonatal calcium metabolism can be negatively affected by a maternal deficiency of vitamin D. In premature infants, bone demineralization can occur and can be corrected with vitamin D supplementation (Specker, 2004).

Maternal vitamin D and fetal growth :

A positive correlation has been seen between maternal and child vitamin D levels. Maternal and infant cord 25(OH)D levels are highly correlated. The high prevalence of vitamin D insufficiency during pregnancy is increasingly recognized that the intrauterine environment can have both immediate and long-lasting effects on health of the offspring. Maternal vitamin D deficiency in early pregnancy has been associated with elevated risk of preterm birth or low birth weight. More recent studies may support the use of vitamin D supplementation during pregnancy to prevent LBW. Extra calcium is required for fetal growth during pregnancy. The majority of this comes from the maternal diet and enhanced intestinal absorption, resulting in a total of around 25–30 g of calcium being transferred to the fetus during the pregnancy, mainly in the last trimester. Maternal total serum calcium levels decline as the pregnancy progresses (Eisman *et al.*, 1989), but during the third trimester the fetus maintains higher serum

calcium levels as a result of active transport of the mineral across the placenta. Maternal 25(OH)D levels do not vary markedly during the pregnancy unless intake or synthesis changes. However, serum $1,25(OH)_2D$ concentrations increase 50–100 per cent above the non-pregnant state during the second trimester and by 100 per cent during the third trimester, largely accounting for the increased intestinal absorption of dietary calcium. 25(OH)D crosses the placental barrier and, at birth, cord blood 25(OH)D levels are directly correlated with maternal levels (Koo and Tsang, 1984).

Prevalence of low vitamin D status during pregnancy:

Vitamin D adequacy depends on both endogenous, UV-induced synthesis and exogenous sources, *i.e.*, diet and supplements. Vitamin D synthesis depends firstly on the level of ultraviolet radiation with this in turn depending on latitude and altitude, time of the year and time of the day. vitamin D synthesis from ultra violet radiation is dependent upon the amount of skin exposed, skin pigmentation, use of sun protection such as shade, sunscreen and other factors. As for other population groups, pregnant women living at high latitude and low altitude, with dark skin pigmentation or skin usually covered by clothing will be at increased risk of vitamin D deficiency, unless dietary intake is high. Obesity is also considered a risk factor for vitamin D insufficiency because adipose tissue serves as store for 25(OH)D.

Vitamin D supplementation :

It is recommended that women with one or more risk factors for low serum 25(OH)D should be monitored at the beginning of gestation and in mid pregnancy (Datta *et al.,* 2002). A recent review suggested that the optimal 25(OH)D level was between 75–110 nmol/L and that these levels could be maintained with supplementation of 1,800 to 4,000 IU daily of vitamin D_3(26,27). Few studies to date have examined vitamin D supplementation during pregnancy and optimal 25(OH)D levels have not yet been defined (Mallet *et al.*, 1986). A daily dose of 1000 IU/day does not appear to be sufficient to achieve and maintain vitamin D adequacy in women who are vitamin D deficient at the start of pregnancy.

The recent publication of the one Randomized Clinical trial of vitamin D supplementation in pregnancy provides insight into the amount of vitamin D intake to achieve various levels of vitamin D status of 494 women randomized in early pregnancy to vitamin D supplements of 400, 2000, or 4000 IU/day, 350 women were followed to term birth. Intake of vitamin D from food was about 200 IU/day and calcium was about 1000 mg/day. For the groups receiving 2000–4000 IU/day, >80 per cent of subjects achieved a serum 25OHD of >80 nmol/L and both maternal and cord blood 25OHD (Table) was significantly higher than for the group Randomized to 400 IU/day vitamin D. No adverse effects were reported for hypercalcemia, hypocalcemia, hypercalciuria, or parathyroid hormone level (Hollis *et al.*, 2011).

Vitamin D status during pregnancy and the effect on fetal weight :

Immunity :

$1,25(OH)_2D$ has effects on immune function within both the innate and adaptive immune systems. During pregnancy, a key requirement for the maternal immune system is the development of immune tolerance to the fetus. Within the placenta, $1,25(OH)_2D$ can function as an intracrine regulator of CAMP (LL37) in trophoblasts, and may thus provide a novel mechanism for activation of innate immune responses in the placenta, assisting the pregnancy (Ponsonby *et al*., 2010).

Bone formation :

There was a positive correlation between the maternal 25(OH)D level and the fetal metaphyseal crosssectional area, with the latter 5 per cent and 14 per cent greater in fetuses of mothers who were vitamin D insufficient (serum 25(OH)D 25-50 nmol/L) and vitamin D deficient (serum 25(OH)D < 25 nmol/L) compared to vitamin D sufficient mothers (serum 25(OH)D > 50 nmol/L) (Mahon *et al.*, 2009).

Birth weight :

Low maternal plasma 25OHD in pregnancy may influence the growth and bone mineral accrual of the offspring during fetal life. Positive associations have been reported between maternal vitamin D status in pregnancy and birth weight, birth length, length. Observational studies of vitamin D status during pregnancy and physical characteristics of the offspring are few and provide conflicting results. One study found pregnancies of mothers with low vitamin D status were shorter (by 0.7 week) and the babies had poorer intrauterine long bone growth, while in other studies, offspring had lower birth

weight (Mannion *et al.*, 2006). However, another study found the opposite, with babies of vitamin D deficient mothers being both heavier and longer, compared to the offspring of vitamin D-sufficient mothers (Scholl and Chen, 2009).

Birth defects :

Low maternal vitamin D status may slow neonatal cardiac development (Weiler *et al.*, 2005) and alter brain morphology with changes in the latter persisting into adulthood. Further, maternal vitamin D deficiency can result in maternal secondary hyperparathyroidism, which may lead to transitory hypocalcemia and hyperparathyroidism in the neonate (Stevens *et al.*, 2000).

Vitamin D deficiency in LBW :

Rickets or osteopenia may present in the newborn infant in cases of decreased skeletal mineralization due to severe vitamin D deficiency. Kovacs (2008) suggested that an infant's bone mass may be related to the vitamin D status of the mother, because the fetus utilizes maternal sources of 25(OH)D to synthesize 1,25$(OH)_2$D. Maternal vitamin D requirements increase during pregnancy. Maternal 25(OH)D concentrations tend to fall during the third trimester.

Excess of vitamin D :

Excess vitamin D administration during pregnancy could also potentially be of concern. Rats had adverse changes in elastin content and organization in the aorta consistent with increased later risk of hypertension when received very high-dose vitamin D during gestation and early development (considerably higher than would be administered to humans). (Norman *et al.*, 2002). In two studies on pigs conducted by Toda *et al.* (1985a) and Toda *et al.* (1985b), vitamin D administration (serum 25(OH)D) levels, approximating recommended for human, was associated with coronary lesions in offspring at six weeks.

Studies :

Study of Heckmatt *et al.* (1979) indicates that vitamin D deficiency is especially significant during pregnancy, as it has been linked to the fetus because of its dependence on maternal consumption, absorption and metabolism of dietary sources. Scholl and Chen (2009) found a linear trend between maternal dietary vitamin D and infant birth weight. Thus, maternal consumption of vitamin D can show positive health benefits for infant birth weight. Marya *et al.* (1981) showed that infants of mothers who received 15,000 μg (600,000 IU) of vitamin D during the seventh and eighth months, of pregnancy had the highest birth weight. Follow-up at 4-7 months of pregnancy assessed 24-hour and 3-day food recall for vitamin D; infant birth weight was obtained from medical records. After controlling for maternal height, weight, number of adults and preschoolers in the household, smoking status and infant gestational age and sex, maternal dietary vitamin D at 4 months was associated with an increase in birth weight of 71 g (Namgung *et al.*, 1993). Another study showed low vitamin D consumption was associated with lower birth weight (Namgung *et al.*, 1994). Mannion *et al.* (2006), comparing growth parameters in newborn infants with the maternal intakes of milk and vitamin D during pregnancy, found an association between vitamin D intake during pregnancy and birth weight. They reported with every additional 40 IU (1μg) of maternal vitamin D intake, there was an associated 11-g increase in birth weight. Fetal calcium concentrations and bone growth are likely influenced by maternal vitamin D status. Animal experiments have demonstrated that low prenatal vitamin D_3 status negatively influences fetal skeletal growth (Rummens *et al.*, 2002). Brooke *et al.* (1980) found that infants born to mothers who had not received vitamin D supplementation had larger fontanelles when compared with those born to mothers supplemented with 25 μg (1,000 IU)/day of vitamin D_2. Administration of 25μg (1,000 IU)/day of vitamin D to vitamin D-deficient Asian women during the third trimester resulted in a lower proportion of neonates with low birth weight compared to the group who received placebo (Maxwell *et al.*, 1981).

Season based studies :

Paunier *et al.* (1978) examined vitamin D and calcium status of forty mothers and their term infants at delivery during the winter months.Calcium concentrations in infants on day four were found to be significantly lower among infants whose mothers consumed <3.75μg (150 IU)/day of vitamin D, compared with those whose mothers consumed >12.5 μg (500 IU)/day of vitamin D during pregnancy. Namgung *et al.* (1994) demonstrated that bone mineral content (BMC) of winter-born infants in Korea was higher than that of summer-born infants

and speculate that maternal vitamin D status during early pregnancy was the influencing factor on fetal bone mineralization while annual periodicity of birth weight, with the heaviest births occurring in October and the lightest in May, has been shown, which reflects the known seasonal variation in 25(OH)D levels (McGrath *et al*., 2005). Infants born during the summer months, had lower birth weights when compared with infants born in spring winter months when 25(OH)D concentrations are highest. (Selvin and Janerich, 1971). American studies have demonstrated lower BMC in infants born in summer compared with winter-born neonates (Wohlfahrt, 1998). The difference in BMC was postulated by the authors to be influenced by different maternal vitamin D_3 status in summer months compared with winter (Mallet, 1986).

Thus birth weight demonstrated by the above studies with a known variation in vitamin D status may indicate a link between season, vitamin D status and birth weight, which may also have effects on skeletal, neurological, and cognitive development of the fetus. On the other hand, Mallet *et al*.(1986) examined relationships between maternal vitamin D status and mean or low birth weight and found no association. McGrath *et al*. (2005) found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length.

Conclusion :

Basic function of vitamin D is related to calcium homeostasis and bone development but emerging evidence suggests that adequate maternal vitamin D status could play important roles in ensuring proper fetal and placental development and proper immune response and function during pregnancy, although its importance and the relative effect on the body is not clearly understood.

Maternal hypovitaminosis D during pregnancy is quite common, because the fetus relies on maternal sources of 25(OH)D to synthesize calcitriol and thus, low maternal 25(OH)D may lead to reduced osteoblastic activity and long bone growth of the fetus. Vitamin D supplementation may affect infant anthropometric measurements and because of the tight relationship between body weight, height, and bone mass, it may also ultimately affect infant skeletal parameters. Maternal vitamin D insufficiency may predispose the child to a number of chronic diseases. The evidence for possible adverse offspring health outcomes resulting from low maternal vitamin D status in pregnancy is present. Women at risk of vitamin D deficiency should be monitored and treated during pregnancy for vitamin D deficiency. LBW continues to be a problem of concern as disorders related to LBW and preterm birth are the leading causes of infant mortality. Studies investigating vitamin D requirements in pregnancy are needed to derive guidelines for general practitioners, midwives, and obstetricians involved in antenatal care and for public education.

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